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FIELD OF THE INVENTION

The present invention relates to new compounds; to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of said compounds and to the use of intermediates in the preparation thereof.

BACKGROUND OF THE INVENTION

Pain sensation in mammals is due to the activation of the peripheral terminals of a specialized population of sensory neurons known as nociceptors. Capsaicin, the active ingredient in hot peppers, produces sustained activation of nociceptors and also produces a dose-dependent pain sensation in humans. Cloning of the vanilloid receptor 1 (VR1 or TRPV1) demonstrated that VR1 is the molecular target for capsaicin and its analogues. (Caterina,M.J., Schumacher,M.A., et.al. Nature 1997 v.389 p 816-824). Functional studies using VR1 indicate that it is also activated by noxious heat and that the threshold for activation can be lowered below normal body temperature by a reduction of the extracellular pH value (acidification) and by other inflammatory mediators Tominaga,M., Caterina,M.J. et.al. Neuron 1998 v.21, p.531-543). Expression of VR1 is also regulated after peripheral nerve damage of the type that leads to neuropathic pain. These properties of VR1 make it a highly relevant target for pain and for diseases involving inflammation. Agonists of the VR1 receptor can act as analgesics, but the usefulness of agonists, such as capsaicin and its analogues, is limited by their pungency, neurotoxicity and induction of hypothermia. Pain-evoking stimuli activate the VR1 receptor and agents that block the activity of VR1 have also shown analgesic activity in animals.

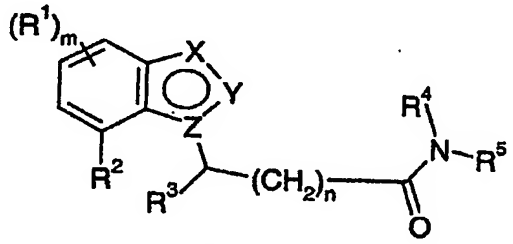
Compounds with VR1 blocker activity are believed to be of potential use for the treatment or prophylaxis of disorders such as pain, especially that of inflammatory or traumatic origin such as arthritis, fibromyalgia, low back pain and post-operative pain. (Walker et al J Pharmacol Exp Ther. 2003 Jan; 304(1):56-62), or visceral pains such as chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis and the like, and also

neuropathic pain such as sciatia, diabetic neuropathy and HIV neuropathy, and the like (Walker et al *ibid*, Rashid et al J Pharmacol Exp Ther. 2003 Mar;304(3):940-8). These compounds are also believed to be potentially useful for inflammatory disorders like asthma, cough, inflammatory bowel disease (IBD) (Hwang and Oh Curr Opin Pharmacol 2002 Jun; 2(3):235-42). Compounds with VR1 blocker activity are also useful for itch and skin diseases like psoriasis and for gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder (Yiangou et al BJU Int 2001 Jun; 87(9): 774-9, Szallasi Am J Clin Pathol 2002 118: 110-21). VR1 inhibitors are also of potential use for the treatment or prophylaxis of the effects of exposure to VR1 activators like capsaicin or tear gas, acids or heat (Szallasi *ibid*).

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to provide compounds exhibiting an activity at the vanilloid receptor 1 (VR1).

The present invention provides a compound of formula I



(I)

wherein:

R^1 is H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 or $CONR^6R^7$;

m is 1, 2, 3 or 4;

R^2 is H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 or $CONR^6R^7$;

X, Y and Z are each independently C, CR^6, N or NR^6;

R^3 is H or C_{0-4}alkyl;

n is 0, 1, 2 or 3;

R^4 is H or C_{0-4}alkyl;

R^5 is H, C_{1-10}alkyl, C_{5-6}aryl, C_{3-7}cycloalkyl, C_{5-6}heteroaryl, whereby any aryl or cycloalkyl may be fused with heteroaryl, C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl;

and R^4 and R^5 may be substituted with one or more A; and

A is H, OH, NO_2, NH_2, CO, O(CO), halo, C_{1-6}alkyl, NR^6R^7, C_{1-6}haloalkyl, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 or $CONR^6R^7$;

R^6 and R^7 are each independently H or C_{1-6}alkyl;

or salts, solvates or solvated salts thereof,

with the proviso the compound is not 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide and 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide.

One embodiment of the invention relates to the compound of formula I wherein R^1 is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl;

m is 1 or 2;

R^2 is H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl or C_{1-6}haloalkyl;

X, Y and Z are each independently C, N and NR^6;

R^3 is H or C_{0-4}alkyl;

n is 0, 1 or 2;

R^4 is H;

R^5 is H, C_{1-10}alkyl, C_{5-6}aryl, whereby any aryl may be fused with heteroaryl;

and R^4 and R^5 may be substituted with one or more A; and

A is H, OH, halo, C_{1-6}alkyl, NR^6R^7, C_{1-6}haloalkyl or C_{1-6}alkylOC_{0-6}alkyl;

R^6 and R^7 are each independently H or C_{1-6}alkyl.

The number of substituents of R^1 is designated by the term m. The substituent R^1 is selected from the group consisting of H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 or $CONR^6R^7$.

In one embodiment of the invention R^1 is selected from the group consisting of H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}haloalkyl and m is 1 or 2.

R^2 may be selected from the group consisting of H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 and $CONR^6R^7$.

In one embodiment of the invention R^2 is H, NO_2, NH_2 or halo.

X, Y and Z are atoms in an aromatic 5-membered ring as shown in the structure of the compound of formula I.

In one embodiment of the invention X, Y and Z are independently selected from the group consisting of C, CR^6, N and NR^6.

In another embodiment of the invention X and Z are N and Y is CR^6.

R^3 may be H or C_{0-4}alkyl. In one embodiment of the invention R^3 is H.

The length of the alkyl chain in the structure of formula I is designated by the term n. n may be 0, 1, 2 or 3. In one embodiment of the invention n is 0.

R^4 and R^5 are substituents on the nitrogen atom. In one embodiment of the invention R^4 is H or C_{0-4}alkyl and R^5 is selected from the group consisting of H, C_{1-10}alkyl, C_{5-6}aryl, C_{3-7}cycloalkyl and C_{5-6}heteroaryl, whereby any aryl or cycloalkyl may be fused with heteroaryl, C_{3-7}cycloalkyl and C_{3-7}heterocycloalkyl.

In another embodiment of the invention R^4 is H and R^5 is selected from the group consisting of H, C_{1-10}alkyl and C_{5-6}aryl, whereby any aryl may be fused with heteroaryl.

Further, R^4 and R^5 may be substituted with one or more A.

In one embodiment of the invention A is selected from the group consisting of H, OH, NO_2, NH_2, CO, O(CO), halo, C_{1-6}alkyl, NR^6R^7, C_{1-6}haloalkyl, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 and $CONR^6R^7$.

In another embodiment of the invention A is selected from the group consisting of H, halo, C_{1-6}alkyl, NR^6R^7, C_{1-6}haloalkyl and C_{1-6}alkylOC_{0-6}alkyl.

A further embodiment of the invention relates to compounds selected from the group consisting of

2-Benzoimidazol-1-yl-*N*-(3-trifluoromethyl-phenyl)-propionamide,

2-Benzoimidazol-1-yl-*N*-(3-chloro-4-fluoro-phenyl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(3-fluoro-4-methyl-phenyl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(3,4-difluoro-phenyl)-acetamide,

2-(4-Methyl-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,

2-(4,5-Difluoro-benzoimidazol-1-yl)-*N*-(3-trifluoromethyl-phenyl)-acetamide,

2-(6,7-difluoro-benzoimidazol-1-yl)-*N*-(3-trifluoromethyl-phenyl)-acetamide,

2-(4,5- difluoro-benzoimidazol-1-yl)-*N*-(3-trifluoromethyl-phenyl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(3-dimethylamino-phenyl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(4-tert-butyl-phenyl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(3-trifluoromethyl-benzyl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(4-chloro-benzyl)-acetamide,

2-(1*H*-Benzoimidazol-1-yl)-*N*-(3,5-dimethoxyphenyl)acetamide,

3-Benzoimidazol-1-yl-*N*-(4-tert-butyl-phenyl)-propionamide,

4-Benzoimidazol-1-yl-*N*-(4-tert-butyl-phenyl)-butyramide,

2-Benzoimidazol-1-yl-*N*-(2-methyl-benzothiazol-5-yl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide,

2-(4-Amino-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,

2-(6,7-Difluoro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,

2-(5-fluoro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,

2-(6-fluoro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,

2-(1*H*-benzoimidazol-1-yl)-*N*-heptylacetamide,

2-(5-Fluoro-1*H*-indol-3-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide, and

2-(1-Methyl-1*H*-indol-3-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,

or salts, solvates or solvated salts thereof.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term C_{1-3} alkyl having 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl, i-propyl or *tert*-butyl.

The term 'C_0' means a bond or does not excist. For example when R^3 is C_0alkyl, R^3 is a bond and "arylC_0alkyl" is equivalent with "aryl", "C_2aklylOC_0alkyl" is equivalent with "C_2alkylO".

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C_{2-6}alkenyl" having 2 to 6 carbon atoms and one or two double bonds, may be, but is not limited to vinyl, allyl, propenyl, butenyl, crotyl, pentenyl, or hexenyl, and a butenyl group may for example be buten-2-yl, buten-3-yl or buten-4-yl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term "C_{2-6}alkynyl" having 2 to 6 carbon atoms and one or two trippel bonds, may be, but is not limited to etynyl, propargyl, pentynyl or hexynyl and a butynyl group may for example be butyn-3-yl or butyn-4-yl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocycloalkyl" denotes a 3- to 7-membered, non-aromatic, partially or completely saturated hydrocarbon group, which contains one rings and at least one heteroatom. Examples of said heterocycle include, but are not limited to pyrrolidinyl, pyrrolidonyl, piperidinyl, piperazinyl, morpholinyl, oxazolyl, 2-oxazolidonyl or tetrahydrofuranyl.

In this specification, unless stated otherwise, the term "aryl" refer to an optionally substituted monocyclic or bicyclic hydrocarbon unsaturated aromatic ring system. Examples of "aryl" may be, but are not limited to phenyl and naphthyl.

In this specification, unless stated otherwise, the term "heteroaryl" refer to an optionally substituted monocyclic or bicyclic unsaturated aromatic ring system containing at least one heteroatom selected independently form N, O or S. Examples of "heteroaryl" may be, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl and oxazolyl.

In this specification, unless stated otherwise, the term "arylalkyl" and "heteroarylalkyl" refer to a substituent that is attached via the alkyl group to an aryl or heteroaryl group.

In this specification, unless stated otherwise, the term "halo" and "halogen" may be fluoro, iodo, chloro or bromo.

In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halo as defined above. The term "C_{1-6}haloalkyl" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "C_{1-6}haloalkylO" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts, solvates or solvated salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Co.).

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of formula I.

Methods of Preparation

Another aspect of the present invention provides processes for preparing compounds of formula I, or salts, solvates or solvated salts thereof.

Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). For representative examples of heterocyclic chemistry see for example "Heterocyclic

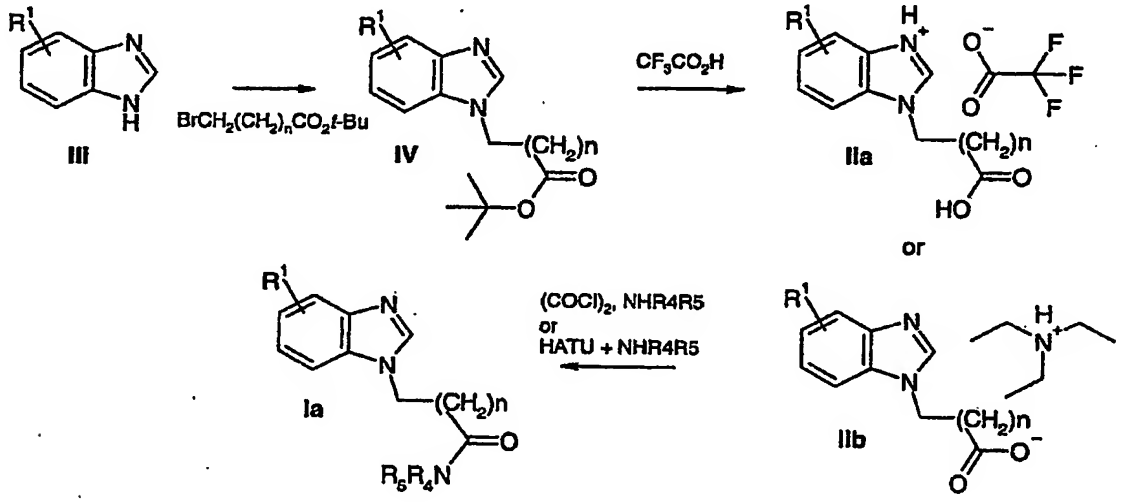
Chemistry", J. A. Joule, K. Mills, G. F. Smith, 3rd ed. Chapman and Hall (1995), p. 189-224 and "Heterocyclic Chemistry", T. L. Gilchrist, 2nd ed. Longman Scientific and Technical (1992), p. 248-282.

The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

One embodiment of the invention relates to processes for the preparation of the compound of formula I according to Methods A and B, wherein R^1 to R^4, unless otherwise specified, are defined as in formula I, comprising;

Another object of the invention are processes for the preparation of the compound of formula I wherein R^1 to R^5, unless otherwise specified, are defined as in formula I, comprising;

Method A

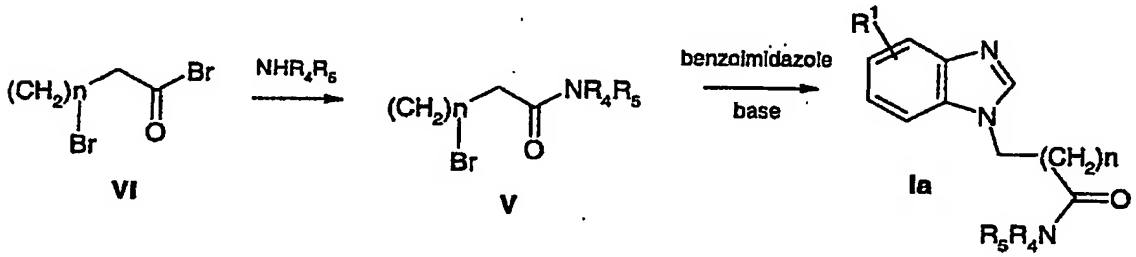


whereby the target compound of formula Ia is obtained from the acid of formula IIa or its deprotonated form IIb, *via* its conversion into an activated form, i.e. either the acyl chloride by treatment with oxalyl chloride or the mixed anhydride by treatment with *O*-(7-azabenzotriazol1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate and futher treatment with an appropriate amine NHR^4R^5. This reaction may be performed in any manner known to the skilled man in the art.

The activation may be performed using any other similar activating reagent like 1,3-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride or 1,1'-carbonyldiimidazole. Suitable solvents to be used for this reaction may be halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxan or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between -30 and 50°C and the reaction time between 1 and 30 h. The intermediate acids of formula IIa may be obtained using 2-steps procedure according to which benzoimidazole of formula III will be alkylated with an appropriate alkylbromide to give an ester of formula IV, and the latter may be deprotected by treatment with trifluoroacetic acid (and optionally converted to the anionic form IIb).

Or,

Method B

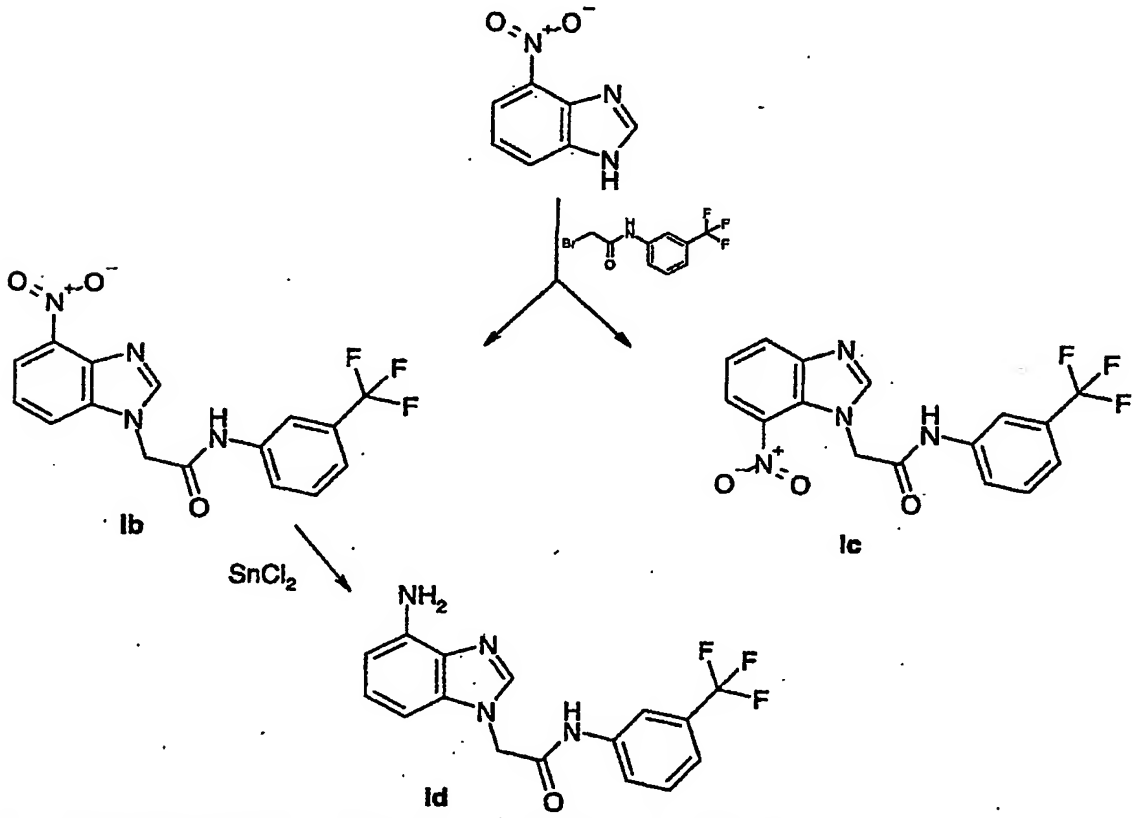


wherein, the target compound of formula Ia is obtained from an alkylbromide of formula V and an appropriate benzimidazole. Suitable solvents to be used for this reaction may be tertiary amides such as dimethylformamide or dimethylacetamide or aromatic compounds such as benzene, toluene and xylene, or ethers such as ethyl ether, tetrahydrofuran and dioxan or alcohols such as methanol, ethanol and propanol, or any mixtures thereof. Bases such as potassium tert-butoxide, sodium methoxide and sodium hydride or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between 0 and 100°C and the reaction time between 1 and 30 h. The intermediate alkylbromides of formula V may be obtained by amination of the corresponding acyl bromides of formula VI.

Substituted benzimidazoles employed in Methods A and B are generally expected to yield mixtures of regioisomers I which in some cases may be separated into pure individual components. This is exemplified in Method C.

One embodiment of the invention relates to a process for purifying mixtures of regioisomers of the compound of formula I, comprising;

Method C



wherein 4-nitrobenzoimidazole is converted to a mixture of 4-nitro- and 7-nitro-regioisomers of formula Ib and Ic, or the nitro derivative is converted to the corresponding amino derivative of formula Id using an appropriate reducing agent.

A further embodiment of the invention relates to compounds

2-bromo-*N*-(3-trifluoromethyl-phenyl)-propionamide,

benzoimidazol-1-yl-acetic acid *tert*-butyl ester,

3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate,

2-bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide,
Synthesis of 4-methyl-1*H*-benzoimidazole,
2-Bromo-*N*-(3-dimethylamino-phenyl)-acetamide,
methyl 3-(1*H*-benzoimidazol-1-yl)propanoate ,
3-(1*H*-benzoimidazol-1-yl)propanoic acid,
methyl 4-(1*H*-benzoimidazol-1-yl)butanoate, and
4-(1*H*-benzoimidazol-1-yl)butanoic acid,
which may be used as intermediates in the preparation of compounds suited for the treatment of VR1 mediated disorders, especially for use as intermediates for the preparation of compounds of formula I.

Pharmaceutical formulation

According to one aspect of the present invention there is provided a pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, or salts, solvates or solvated salts thereof, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers. Suitable daily doses of the compound of formula I in the treatment of a mammal, including man are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

Medical use

Surprisingly, it has been found that the compounds according to the present invention are useful in therapy. The compounds of formula I, or salts, solvates or solvated salts thereof, as well as their corresponding active metabolites, exhibit a high degree of potency and selectivity for individual vanilloid receptor 1 (VR1) groups. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of vanilloid receptor 1 (VR1).

The compounds may be used to produce an inhibitory effect of VR1 in mammals, including man.

VR1 are highly expressed in the peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of VR1 mediated disorders. The compounds of formula I are expected to be suited for the treatment of acute and chronic pain and acute and chronic inflammatory pain. The compound may further be suited for the treatment of chronic neuropathic pain.

Examples of such disorder may be selected from the group comprising of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, inflammatory bowel disease (IBD) and psoriasis.

Further relevant disorders that may be treated using the compounds of formula I may be selected from the group comprising of gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

The compounds of formula I may also be used as antitoxin to treat (over-) exposure to VR1 activators like capsaicin or tear gas, acids or heat.

The compounds may further be used for treatment of tolerance to VR1 activators.

One embodiment of the invention relates to the use of the compound of formula I in therapy.

Another embodiment of the invention relates to the use of the compound of formula I for treatment of VR1 mediated disorders.

A further embodiment of the invention relates to the use of the compound of formula I for treatment of acute and chronic pain disorders

Yet another embodiment of the invention relates to the use of the compound of formula I for treatment of acute and chronic inflammatory pain.

Yet a further embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, for treatment of indications selected form the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

One embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, as hereinbefore defined.

A further embodiment of the invention relates to a pharmaceutical formulation comprising the compound of formula I, as hereinbefore defined, for use in the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

One embodiment of the invention relates to the use of 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide and 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide , in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide or 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide.

A further embodiment of the invention relates to a pharmaceutical formulation comprising 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide or 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide, for use in the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

In the context of the present specification, the term "therapy" and "treatment" includes prevention and prophylaxis, unless there are specific indications to the contrary. The terms "treat","therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "antagonist" and "inhibitor" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with vanilloid receptor activity.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of formula I, or salts, solvates or solvated salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of VR1 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Examples

The invention will now be illustrated by the following non-limiting examples.

General methods

All starting materials are commercially available or described in the literature. The ^1H NMR spectra were recorded on Brucker at 400 MHz. The mass spectra were recorded utilising electrospray (LC-MS; LC:Waters 2790, column XTerra MS C_8 2.5 µm 2.1X30 mm, buffer gradient H_2O+0.1%TFA:CH_3CN+0.04%TFA, MS: micromass ZMD// ammonium acetate buffer) ionisation techniques.

Example 1

2-Benzoimidazol-1-yl-N-(3-trifluoromethyl-phenyl)-propionamide

Part A: Synthesis of 2-bromo-*N*-(3-trifluoromethyl-phenyl)-propionamide

2-Bromopropionyl bromide (430 mg, 2.1 mmol) was added under stirring to a solution of 3-trifluoromethyl-aniline (320 mg, 2.0 mmol) and triethylamine (0.3 mL, 2.1 mmol) in dichloromethane (15 mL). The reaction was stirred for 1 h at ambient temperature and the solvent was evaporated. The crude product was purified by flash chromatography (silica, 20% heptane in ethyl acetate) to afford 2-bromo-*N*-(3-trifluoromethyl-phenyl)-propionamide (0.50 g, 85%).

Mass spectrum (ESI) m/z: 296.9, 297.9.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.0 (d, *J*=7.1 Hz, 3 H), 4.5 (q, *J*=7.1 Hz, 1 H), 7.4 (d, *J*=7.6 Hz, 1 H), 7.5 (t, *J*=7.8 Hz, 1 H), 7.7 (d, *J*=7.9 Hz, 1 H), 7.8 (s, 1 H), 8.2 (s, 1 H).

Part B: Synthesis of the title compound

A solution of potassium *tert*-butoxide (0.25 mL of 1 M solution in THF, 0.25 mmol) was added to a solution of 1*H*-benzoimidazole (30 mg, 0.25 mmol) in anhydrous dioxane (10 mL) and anhydrous DMF (1 mL) under argon at ambient temperature. The mixture was stirred for 5 min before a solution of bromo-*N*-(3-trifluoromethyl-phenyl)-propionamide (59 mg, 0.2 mmol) in anhydrous dioxane (3 mL) was added. The mixture was stirred for 4 h, filtered and concentrated in vacuum. The crude product was purified on a preparative HPLC (XTerra C_8 column 19×300 mm, 0.1 M aqueous NH_4Ac/CH_3CN). Product-containing fractions were pooled and lyophilized to afford 40 mg (60%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.8 (d, *J*=7.1 Hz, 3 H), 5.1 (q, *J*=7.4 Hz, 1 H), 7.2 (m, 4 H), 7.4 (d, *J*=7.1 Hz, 1 H), 7.5 (m, 2 H,) 7.7 (m, 1 H), 7.9 (s, 1 H), 10.2 (s, 1 H).

Example 2

2-Benzoimidazol-1-yl-N-(3-chloro-4-fluoro-phenyl)-acetamide

Part A: Synthesis of benzoimidazol-1-yl-acetic acid *tert*-butyl ester

A solution of potassium *tert*-butoxide (0.6 mmol) in THF (0.6 mL) was added to a solution of 1*H*-benzoimidazole (71 mg, 0.6 mmol) in dioxane (15 mL) under stirring. *tert*-Butyl bromoacetate (97 mg, 0.5 mmol) was added to the white suspension and the mixture was stirred overnight at ambient temperature. The solvents were removed in vacuum and the product was purified on a silica gel column using a gradient of ethyl acetate in heptane) to afford benzimidazol-1-yl-acetic acid *tert*-butyl ester (110 mg, 95%).

Mass spectrum (ESI) m/z: 233.0.

^{1}H NMR (400 MHz, MeOD) δ ppm 1.5 (s, 9 H), 5.0 (s, 2 H), 7.3 (m, 2 H), 7.4 (d, *J*=7.1 Hz, 1 H), 7.7 (d, *J*=6.6 Hz, 1 H), 8.1 (s, 1 H).

Part B: Synthesis of 3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate

Benzoimidazol-1-yl-acetic acid *tert*-butyl ester (110 mg, 0.47 mmol) was dissolved in dichloromethane (3 mL) and trifluoroacetic acid (1 mL) was added. The reaction was

stirred at ambient temperature for 24 h and the solvents were removed to afford 3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate (136 mg, 100%).
Mass spectrum (ESI) m/z: 177.0.
^{1}H NMR (400 MHz, MeOD) δ ppm 5.3 (s, 2 H), 7.5 (m, 2 H), 7.8 (m, 2 H), 9.4 (s, 1 H).

Part C: Synthesis of the title compound
3-Carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate (128 mg, 0.44 mmol) was dissolved in a mixture of oxalyl chloride (0.6 mL) and dichloromethane (3.4 mL). The reaction mixture was stirred for 30 min at ambient temperature and the solvent was evaporated. The residue was dissolved in a mixture of dichloromethane (2.5 mL) and anhydrous THF (2.5 mL) and added to a mixture of 3-chloro-4-fluoro-aniline (17 mg, 0.12 mmol) and *N,N*-(diisopropyl)aminomethylpolystyrene resin (140 mg, Argonaut Technologies, Inc) in anhydrous THF (3 mL). The mixture was shaken overnight. The resin was filtered off, the solvents were evaporated and the crude product was purified on a preparative LC/MS (XTerra C_8 column 19×100 mm, 0.1 M aqueous NH_4Ac/CH_3CN). The pooled fractions were lyophilized to afford 7.2 mg (20%) of the title compound.
Calculated for $C_{15}H_{11}ClFN_3O$ *m/z*: 303.7, found 304.7 $[M+H]^+$.
^{1}H NMR (400 MHz, MeOD) δ ppm 5.2 (s, 2 H), 7.2 (t, *J*=9.1 Hz, 1 H), 7.3 (m, 2 H), 7.5 (m, 1 H), 7.5 (d, *J*=7.1 Hz, 1 H), 7.7 (d, *J*=7.1 Hz, 1 H), 7.8 (dd, *J*=6.6, 2.5 Hz, 1 H), 8.2 (s, 1 H).

Example 3

2-Benzoimidazol-1-yl-N-(3-fluoro-4-methyl-phenyl)-acetamide

The title compound was synthesised according to the procedure described in Example 2, from 3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate and 3-fluoro-4-methyl-aniline.
Yield 12 mg (35%).
Calculated for $C_{16}H_{14}FN_3O$ *m/z*: 283.3, found 284.3 $[M+H]^+$.
^{1}H NMR (400 MHz, MeOD) δ ppm 2.2 (s, 3 H), 5.1 (s, 2 H), 7.1 (m, 2 H), 7.3 (m, 2 H), 7.4 (d, *J*=11.6 Hz, 1 H), 7.5 (d, *J*=8.6 Hz, 1 H), 7.7 (m, 1 H), 8.1 (s, 1 H).

Example 4

2-Benzoimidazol-1-yl-N-(3,4-difluoro-phenyl)-acetamide

The title compound was synthesised according to the procedure described in Example 2, from 3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate and 3,4-difluoroaniline

Yield 9.1 mg (26%).

Calculated for $C_{15}H_{11}F_2N_3O$ *m/z*: 287.2, found 288.3 $[M+H]^+$.

^{1}H NMR (400 MHz, MeOD) δ ppm 5.2 (s, 2 H), 7.3 (m, 4 H), 7.5 (d, *J*=7.1 Hz, 1 H), 7.7 (m, 2 H), 8.2 (s, 1 H).

Example 5

2-Indol-1-yl-N-(3-trifluoromethyl-phenyl)-acetamide

Part A: Synthesis of 2-bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide

Bromoacetyl bromide (1.41 g, 7 mmol) was added under stirring to a solution of 3-trifluoromethyl-aniline (0.77 g, 4.8 mmol) and triethylamine (0.83 mL, 8.2 mmol) in THF (60 mL) at 0 °C. The reaction was stirred for 3 h at 0 °C and the solvent was evaporated. The crude product was purified by flash chromatography (Silica, heptane/ethyl acetate 1:1) to afford 2-bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide (1.35 g, 100%).

Mass spectrum (ESI) m/z: 280.0, 282.0.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.93 (s, 2 H), 7.31 (d, *J*=8.1 Hz, 1 H), 7.44 (t, *J*=7.8 Hz, 1 H), 7.63 (d, *J*=8.1 Hz, 1 H), 7.93 (s, 1 H), 10.57 (s, 1 H).

Part B: Synthesis of title compound

A solution of potassium *tert*-butoxide (0.25 mmol) in THF (0.25 mL) was added to a solution of 1*H*-indole (30 mg, 0.25 mmol) in a mixture of dioxane (6 mL) and DMF (1.5 mL) under argon atmosphere at ambient temperature. The solution was stirred for 5 min before a solution of 2-bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide (0.2 mmol) in DMF (1 mL) was added dropwise. The reaction mixture was stirred overnight at ambient temperature and the solvents were removed in vacuum. The crude product was purified on a preparative LC/MS (XTerra C_8 column 19×100 mm, 0.1 M aqueous NH_4Ac/CH_3CN). The product-containing fractions were pooled and lyophilized to afford 24 mg (38 %) of the title compound.

Calculated for $C_{17}H_{13}F_3N_2O$ *m/z*: 318.3, found 319.0 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.9 (s, 2 H), 6.7 (d, *J*=3.0 Hz, 1 H), 7.0 (s, 1 H), 7.1 (d, *J*=3.0 Hz, 1 H), 7.2 - 7.3 (m, 5 H), 7.4 (m, 1 H), 7.6 (s, 1 H), 7.7 (d, *J*=8.1 Hz, 1 H).

Example 6

2-(4-Methyl-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide

Part A: Synthesis of 4-methyl-1*H*-benzoimidazole

A solution of 3-methylbenzene-1,2-diamine (500 mg, 4.1 mmol) in formic acid (4.5 mL, 120 mmol) was irradiated in a microwave oven for 15 min at 135 °C. The reaction mixture was cooled to ambient temperature and the formic acid was removed under reduced pressure. The residue was dissolved in ethyl acetate (20 mL) and extracted with saturated aqueous $NaHCO_3$ (2×10 mL), water (10 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuum yielding 4-methyl-1*H*-benzoimidazole (519 mg, 96%)

Calculated for $C_8H_8N_2$ *m/z*: 132.07, found 133.13 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.50 (s, 3 H), 6.96 (m, 1 H), 7.06 (m, 1 H), 7.38 (d, J=7.6 Hz, 1 H), 8.15 (s, 1 H), 12.41 (s, 1 H).

Part B: Synthesis of the title compound

The title compound was synthesized in 39% yield (65 mg) according to a procedure described in Example 5, using 4-methyl-1*H*-benzoimidazole (66 mg, 0.5 mmol) and 2-bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide (Example 5, part A) (141 mg, 0.5 mmol).

Calculated for $C_{17}H_{14}F_3N_3O$ *m/z*: 333.11, found 334.07 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.54 (s, 3 H), 5.18 (s, 2 H), 7.01 (d, *J*=7.6 Hz, 1 H), 7.12 (m, 1 H), 7.33 (d, *J*=8.1 Hz, 1 H), 7.42 (d, *J*=7.6 Hz, 1 H), 7.57 (t, *J*=8.1 Hz, 1 H), 7.77 (d, *J*=8.1 Hz, 1 H), 8.06 (s, 1 H), 8.18 (s, 1 H), 10.77 (s, 1 H).

Example 7

2-(4,5-Difluoro-benzoimidazol-1-yl)-N-(3-trifluoromethyl-phenyl)-acetamide and *2-(6,7-difluoro-benzoimidazol-1-yl)-N-(3-trifluoromethyl-phenyl)-acetamide* (mixture of 4,5- and 6,7-difluoro- regioisomers)

2-Bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide (see Example 5, Part A) (29 mg, 0.1 mmol) and 4,5-difluoro-1*H*-benzoimidazole (23 mg, 0.15 mmol) were added sequentially to a solution of potassium *tert*-butoxide (0.18 mL of 1 M solution in THF, 0.18 mmol,) in DMF (1.5 mL) under argon atmosphere. The reaction was stirred at ambient temperature overnight. The product was purified on a preparative LC/MS (XTerra C_8 column 19×100 mm, 0.1 M aqueous NH_4Ac/CH_3CN) affording the title compounds in 2:1 ratio.
Calculated for $C_{16}H_{10}F_5N_3O$ *m/z*: 355.27, found 356.0 $[M+H]^+$.

Example 8

2-Benzoimidazol-1-yl-N-(3-dimethylamino-phenyl)-acetamide

Part A: 2-Bromo-*N*-(3-dimethylamino-phenyl)-acetamide

Bromoacetyl bromide (21 μL, 0.24 mmol) was added to a suspension of *N,N*-dimethyl-benzene-1,3-diamine (27 mg, 0.2 mmol) and PS-diisopropylethylamine (170 mg of the resin, 0.6 mmol) in anhydrous THF (1.5 mL). The mixture was stirred overnight at ambient temperature. The resin was filtered off and the solution containing 2-bromo-*N*-(3-dimethylamino-phenyl)-acetamide was used directly in the next step (see Part B).

Part B: The title compound was synthesised according to the procedure described in Example 7, from 2-bromo-*N*-(3-dimethylamino-phenyl)-acetamide and 1*H*-benzoimidazole.
Calculated for $C_{17}H_{18}N_4O$ *m/z*: 294.3, found 295.3 $[M+H]^+$.

Example 9

2-Benzoimidazol-1-yl-N-(4-tert-butyl-phenyl)-acetamide

The title compound was synthesised according to the procedure described in Example 8 (Part B), from 1*H*-benzoimidazole and 2-bromo-*N*-(4-*tert*-butyl-phenyl)-acetamide. The latter was synthesized according to the procedure described in Example 8 (Part A) from bromoacetyl bromide and 4-*tert*-butyl-aniline.
Calculated for $C_{19}H_{21}N_3O$ *m/z*: 307.3, found 308.4 $[M+H]^+$.

Example 10

2-Benzoimidazol-1-yl-N-(3-trifluoromethyl-benzyl)-acetamide

O-(7-Azabenzotriazol1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (80 mg, 0.21 mmol) was added under stirring to a solution of 3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate (Example 2 part B) (32 mg, 0.2 mmol) and *N*-methyl morpholine (66 µL, 0.6 mmol) in acetonitrile (1 mL). After 5 min 3-trifluoromethyl-benzylamine (0.2 mmol, 35 mg) was added and the mixture was shaken overnight at ambient temperature. Purification was performed on a preparative LC/MS (XTerra C_8 column 19×100 mm, 0.1 M NH_4OAc/CH_3CN). Product-containing fractions were pooled and lyophilized thus affording 8.3 mg of the title compound (12%).

Calculated for $C_{17}H_{14}F_3N_3O$ *m/z*: 333.32, found 334.1 $[M+H]^+$.

Example 11

2-Benzoimidazol-1-yl-N-(4-chloro-benzyl)-acetamide

The title compound was synthesized according to a procedure described in Example 10 starting from 3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate (Example 2, Part B) and 4-chloro-benzylamine

Calculated for $C_{16}H_{14}ClN_3O$ *m/z*: 299.76, found 301.1 $[M+H]^+$.

Example 12

2-(1H-Benzoimidazol-1-yl)-N-(3,5-dimethoxyphenyl)acetamide

The title compound was synthesized according to a procedure described in Example 10 starting from 3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate (Example 2 part B) and 3,5-dimethoxy-aniline.

Calculated for $C_{17}H_{17}N_3O_3$ *m/z*: 311.34, found 311.88 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ ppm 3.69 (s, 6 H), 5.14 (s, 2 H), 6.23 (t, *J*=2.3 Hz, 1 H), 6.82 (d, *J*=2.0 Hz, 2 H), 7.22 (m, 2 H), 7.51 (d, *J*=7.6 Hz, 1 H), 7.66 (dd, *J*=7.3, 1.3 Hz, 1 H), 8.21 (s, 1 H), 10.41 (s, 1 H).

Example 13

3-Benzoimidazol-1-yl-N-(4-tert-butyl-phenyl)-propionamide

Part A: Synthesis of methyl 3-(1*H*-benzoimidazol-1-yl)propanoate

To a solution of 1*H*-benzoimidazole (1.21 g, 10 mmol) in dry DMF (30 mL) potassium *tert*-butoxide solution in THF (1 M, 10.5 mL, 10.5 mmol) was added under stirring at ambient temperature. After 15 min methyl 3-bromopropanoate (1.1 mL, 10 mmol) was added drop-wise and the reaction mixture was stirred for 16 h. The mixture was quenched by addition of methanol (1 mL) and formic acid (1 mL), and concentrated in vacuum. The residue was treated with a mixture of ethyl acetate and water (25 and 5 mL, respectively), the organic phase was separated and washed with saturated aqueous $NaHCO_3$. The solvent was removed under reduced pressure and the crude product was purified on a pre-packed 12 g silica column (RediSep™, Isco, Inc.) using ethyl acetate as the eluent.

Yield 0.56 g (27%). Calculated for $C_{11}H_{12}N_2O_2$ *m/z*: 204.09, found 204.97 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.92 (t, *J*=6.3 Hz, 2 H), 3.67 (s, 3 H), 4.57 (t, *J*=6.3 Hz, 2 H), 7.36 (m, 2 H), 7.45 (m, 1 H), 7.87 (m, 1 H), 8.36 (s, 1 H).

Part B: Synthesis of 3-(1*H*-benzoimidazol-1-yl)propanoic acid

To a solution of methyl 3-(1*H*-benzoimidazol-1-yl)propanoate (0.56 g, 2.7 mmol) in methanol (0.5 mL) an aqueous solution of NaOH (2M, 0.5 mL) was added under stirring at ambient temperature. Upon consumption of the starting material (15 min), methanol was removed from the reaction mixture under reduced pressure. Aqueous HCl (1 M, 1 mL) was added followed by evaporation of the volatiles. To the residue dichloromethane (30 mL) containing triethylamine (1 mL) was added and the slurry was filtered. The filtrate was concentrated and the crude product was purified on a pre-packed 12 g silica column (RediSep™, Isco, Inc.) using 3% methanol and 1% triethylamine in dichloromethane as an eluent. Product-containing fractions were pooled, concentrated under reduced pressure, co-evaporated with ethyl acetate (3×10 mL) and dried under reduced pressure at 40 °C for 24 h.

Yield 0.34 g (65%). Calculated for $C_{10}H_{10}N_2O_2$ *m/z*: 190.07, found 190.91 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ ppm 2.81 (t, *J*=6.8 Hz, 2 H), 4.45 (t, *J*=6.8 Hz, 2 H), 7.22 (m, 2 H), 7.61 (dd, *J*=2.0, 1.0 Hz, 1 H), 7.63 (m, 1 H), 8.17 (s, 1 H).

Part C. The title compound was synthesized according to a procedure described in Example 10 starting from 3-benzoimidazol-1-yl-propanoic acid and 4-*tert*-butyl-aniline. Calculated for $C_{16}H_{23}N_3O$ *m/z*: 321.18, found 322.1 $[M+H]^+$.

Example 14

4-Benzoimidazol-1-yl-N-(4-tert-butyl-phenyl)-butyramide

Part A: Synthesis of methyl 4-(1*H*-benzoimidazol-1-yl)butanoate

Methyl 4-(1*H*-benzoimidazol-1-yl)butanoate was prepared according to the procedure described in Example 13 (Part A) from 1*H*-benzoimidazole (1.21 g, 10 mmol) and methyl 4-bromobutanoate (1.3 mL, 10 mmol) in the presence of tetra-*n*-butylammonium iodide (300 mg, 0.8 mmol). Purification was performed using 2% methanol in dichloromethane. Yield 1.41 g (65%). Calculated for $C_{12}H_{14}N_2O_2$ *m/z*: 218.11, found 219.98 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.22 (m, 2 H), 2.35 (t, *J*=6.6 Hz, 2 H), 3.67 (s, 3 H), 4.31 (t, *J*=7.1 Hz, 2 H), 7.33 (m, 2 H), 7.46 (m, 1 H), 7.83 (m, 1 H), 8.14 (s, 1 H).

Part B: Synthesis of 4-(1*H*-benzoimidazol-1-yl)butanoic acid

The title compound was prepared according to the procedure described in Example 13 (Part B) starting from methyl 4-(1*H*-benzoimidazol-1-yl)butanoate (1.41 g, 6.5 mmol). Yield 1.1 g (54%). Calculated for $C_{11}H_{12}N_2O_2$ *m/z*: 204.09, found 204.91 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ ppm 2.01 (m, 2 H), 2.22 (t, *J*=7.3 Hz, 2 H), 4.26 (t, *J*=7.1 Hz, 2 H), 7.22 (m, 2 H), 7.62 (dd, *J*=18.2, 8.1 Hz, 2 H), 8.20 (s, 1 H), 12.11 (s, 1 H).

Part C. The title compound was synthesized according to a procedure described in Example 10 starting from 4-benzoimidazol-1-yl-butyric acid and 4-*tert*-butyl-aniline. Calculated for C16H23N3O m/z: 335.20, found 336.1 [M+H]+.

Example 15

2-Benzoimidazol-1-yl-N-(2-methyl-benzothiazol-5-yl)-acetamide

2-Methyl-benzothiazol-5-ylamine (32 mg, 0.2 mmol) and bromoacethyl bromide were added to a suspension of (*N,N*-diisopropyl)aminomethylpolystyrene resin (170 mg) in anhydrous THF (2 mL) and the reaction mixture was shaken for 4 h at ambient temperature. The resin was then filtered off. 1*H*-benzoimidazole (35 mg, 0.3 mmol) and potassium *tert*-butoxide (0.36 mL of 1 M solution in THF, 0.36 mmol,) were added and the mixture was stirred at 55 °C for 24 h. The crude product was purified on a preparative

LC/MS (XTerra C_8 column 19×100 mm, 0.1 M aqueous NH_4Ac/CH_3CN). The pooled fractions were lyophilized to afford 4 mg (6 %) of the title compound.
Calculated for $C_{17}H_{14}N_4OS$ *m/z*: 322.39, found 323.0 $[M+H]^+$.

Example 16

2-Benzoimidazol-1-yl-N-(3-trifluoromethyl-phenyl)-acetamide

A solution of potassium *tert*-butoxide (1.7 mL of 1 M solution in THF, 1.7 mmol,) was added to a solution of 1*H*-benzoimidazole (165 mg, 1.4 mmol) in anhydrous THF (3 mL). The reaction mixture was stirred for 20 min at ambient temperature. 2-Bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide (example 5 part A) was added (261 mg, 0.93 mmol) and the mixture was stirred at 55 °C for subsequent 24 h. The crude product was purified on a preparative HPLC (XTerra C_8 column 19×300 mm, 0.1 M aqueous NH_4Ac/CH_3CN). The pooled fractions were lyophilized to afford 81 mg (27 %) of the title compound.
Calculated for $C_{16}H_{12}F_3N_3O$ *m/z*: 319.29, found 320.0 $[M+H]^+$.
1H NMR (400 MHz, MeOH) δ ppm 5.2 (s, 2 H), 7.3 (m, 2 H), 7.4 (d, *J*=7.6 Hz, 1 H), 7.5 (m, 2 H), 7.7 (d, *J*=7.1 Hz, 1 H), 7.8 (d, *J*=8.6 Hz, 1 H), 8.0 (s, 1 H), 8.2 (s, 1 H).

Example 17

2-(7-Nitro-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide

Potassium *tert*-butoxide (195 mg, 1.73 mmol,) was added to a stirred solution of 4(7)-nitro-1*H*-benzoimidazole (270 mg, 1.65 mmol) in DMF (5.5 mL). After 10 min 2-bromo-*N*-[3-(trifluoromethyl)phenyl]acetamide (466 mg, 1.65 mmol) was added and the mixture was stirred for 3 h at ambient temperature. The solvent was removed under reduced pressure and the residue was treated with ethyl acetate and 0.5 M phosphate buffer (pH 7) (25 mL of each). The organic layer was separated, washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated to leave a mixture of 4- and 7-nitro regioisomers. Separation of the mixture was performed on preparative HPLC (XTerra C_8 column 19×300 mm, 0.1 M NH_4OAc/CH_3CN). Product-containing fractions were pooled and lyophilised affording the pure individual regioisomers.
The major product: 2-(4-nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide was obtained in 73% (435 mg) yield.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 5.36 (s, 2 H), 7.45 (m, 2 H), 7.58 (t, *J*=7.8 Hz, 1 H), 7.77 (d, *J*=8.6 Hz, 1 H), 8.06 (bs, 2 H), 8.08 (s, 1 H), 8.55 (s, 1 H), 10.83 (s, 1 H).

The title compound was obtained as a minor product (45.3 mg, 8%). Calculated for $C_{16}H_{11}F_3N_4O_3$ *m/z*: 364.08, found 365.03 $[M+H]^+$.
^{1}H NMR (400 MHz, CD_3CN) δ ppm 5.43 (s, 2 H), 7.43 (m, 2 H), 7.56 (t, *J*=8.1 Hz, 1 H), 7.71 (d, *J*=8.1 Hz, 1 H), 7.98 (s, 1 H), 8.03 (dd, *J*=8.1, 0.76 Hz, 1 H), 8.15 (dd, *J*=7.8, 1.0 Hz, 1 H), 8.45 (s, 1 H), 10.76 (s, 1 H).

Example 18

2-(4-Amino-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide

2-(4-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide (60 mg, 0.17 mmol) (see Example 17) was dissolved in ethanol (1.44 mL) and tin(II) chloride (192 mg, 0.85 mmol) was added. The reaction mixture was stirred at 70 °C for 16 h and then poured onto a mixture of ice and saturated aqueous $NaHCO_3$ (20 mL). The basic solution was extracted with ethyl acetate (3×10 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The purification of the crude product was performed by preparative HPLC (XTerra C_8 column 19×300 mm, 0.1 M NH_4OAc/CH_3CN). Product-containing fractions were pooled and lyophilised affording the title compound (11.3 mg, 20%).
Calculated for $C_{16}H_{13}F_3N_4O$ *m/z*: 334.10, found 335.09 $[M+H]^+$.
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 5.07 (s, 2 H), 5.24 (s, 2 H), 6.37 (dd, *J*=7.6, 0.8 Hz, 1 H), 6.64 (dd, *J*=8.0, 0.63 Hz, 1 H), 6.90 (t, *J*=7.8 Hz, 1 H), 7.42 (d, *J*=7.8 Hz, 1 H), 7.57 (t, *J*=8.0 Hz, 1 H), 7.77 (m, 1 H), 7.99 (s, 1 H), 8.06 (s, 1 H), 10.74 (s, 1 H).

Example 19

2-(6,7-Difluoro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide
To a suspension of 4,5-difluoro-1*H*-benzoimidazole (20 mg, 0.13 mmol) in toluene (260 μL), triethylamine (18 μL, 0.13 mmol) and 2-bromo-*N*-[3-(trifluoromethyl)phenyl]acetamide (37 mg, 0.13 mmol) were added. The reaction mixture was microwave-irradiated in a sealed vial at 120 °C for 30 min. The vial was cooled, opened and the contents dissolved in 20 mL ethyl acetate. The solution was washed with

water (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product was performed on flash silica column using neat ethyl acetate to yield the title compound (11.3 mg, 25%). Calculated for $C_{16}H_{10}F_5N_3O$ *m/z*: 355.07, found 355.84 $[M+H]^+$.

^1H NMR (400 MHz, MeOD) δ ppm 5.31 (s, 2 H), 7.20 (ddd, *J*=11.4, 9.0, 7.5 Hz, 1 H), 7.40 (d, *J*=7.8 Hz, 1 H), 7.47 (ddd, *J*=8.9, 3.7, 1.3 Hz, 1 H), 7.52 (t, *J*=8.1 Hz, 1 H), 7.79 (d, *J*=8.8 Hz, 1 H), 7.96 (s, 1 H), 8.20 (s, 1 H).

Example 20

2-(5-fluoro-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide and *2-(6-fluoro-1H-benzoimidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]acetamide* (mixture of 5- and 6-regioisomers)

Synthesis was performed as described in Example 19 using 5(6)-fluoro-1*H*-benzoimidazole (68 mg, 0.5 mmol). Yield 28 mg (17%). Calculated for $C_{16}H_{11}F_4N_3O$ m/z: 337.08, found 337.83 $[M+H]^+$.

Example 21

2-(1H-benzoimidazol-1-yl)-N-heptylacetamide

O-(7-Azabenzotriazol1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (80 mg, 0.21 mmol) was added under stirring to a solution of 1*H*-benzoimidazol-1-ylacetic acid triethylammonium salt (55.5 mg, 0.2 mmol) and *N*-methyl morpholine (66 μL, 0.6 mmol) in acetonitrile (1 mL). After 5 min 1-heptylamine (30 μL, 0.2 mmol) was added and mixture was stirred at ambient temperature for 3 h. The solvent was evaporated, the residue was dissolved in ethyl acetate (15 mL) and extracted with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL) then dried over anhydrous Na_2SO_4 and concentrated. Purification of the crude product was performed by preparative HPLC (XTerra C_8 column 19×300 mm, 0.1 M NH_4OAc/CH_3CN). Product-containing fractions were pooled and lyophilised affording the title compound (43.7 mg, 80%). Calculated for $C_{16}H_{23}N_3O$ *m/z*: 273.18, found 274.03 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ ppm 0.85 (m, 3 H), 1.26 (m, 8 H), 1.41 (m, 2 H), 3.07 (m, 2 H), 4.88 (s, 2 H), 7.20 (m, 2 H), 7.42 (m, 1 H), 7.64 (m, 1 H), 8.14 (s, 1 H), 8.27 (t, *J*=5.6 Hz, 1 H).

Example 22

2-(5-Fluoro-1H-indol-3-yl)-N-[3-(trifluoromethyl)phenyl]acetamide

The title compound was synthesized in 57% yield (38.5 mg) according to a procedure described in Example 21 starting from (5-fluoro-1*H*-indol-3-yl)-acetic acid and 3-trifluoromethyl-aniline.

Calculated for $C_{16}H_{23}N_3O$ *m/z*: 336.09, found 336.88 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ 3.73 (s, 2 H), 6.91 (m, 1 H), 7.34 (m, 4 H), 7.53 (t, *J*=8.1 Hz, 1 H), 7.78 (d, *J*=8.1 Hz, 1 H), 8.09 (s, 1 H), 10.42 (s, 1 H), 11.03 (s, 1 H).

Example 23

2-(1-Methyl-1H-indol-3-yl)-N-[3-(trifluoromethyl)phenyl]acetamide

The title compound was synthesized in 62% yield (41.1 mg) according to a procedure described in Example 21 starting from (1-methyl-1*H*-indol-3-yl)-acetic acid and 3-trifluoromethyl-aniline.

Calculated for $C_{16}H_{23}N_3O$ *m/z*: 332.11, found 332.89 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ ppm 3.74 (s, 2 H), 3.75 (s, 3 H), 7.01 (m, 1 H), 7.14 (m, 1 H), 7.25 (s, 1 H), 7.38 (t, *J*=8.1 Hz, 2 H), 7.53 (t, *J*=7.8 Hz, 1 H), 7.60 (d, *J*=8.1 Hz, 1 H), 7.79 (d, *J*=8.6 Hz, 1 H), 8.10 (s, 1 H), 10.43 (s, 1 H).

Pharmacology

DRGs were dissected out from adult Sprague Dawley rats (100-300 gr), and placed on ice in L15 Leibovitz medium. The ganglia were enzyme treated with Collagenase 80U/ml+ Dispase 34 U/ml dissolved in DMEM +5% serum, overnight at 37 °C. The next day, cells were triturated with fire polished pasteur pipettes, and seeded in the center of 58 mm diameter Nunc cell dishes coated with Poly-D Lysine (1 mg/mL). The DRGs were cultured in a defined medium without foetal bovine serum, containing Dulbecco's MEM / NUT MIX F-12 (1:1) without L-glutamine but with pyridoxine, 6 mg/mL D(+)-Glucose, 100 μg/mL apo-transferrin, 1 mg/mL BSA, 20 μg/mL insulin, 2 mM L-glutamine, 50 IU/ mL Penicillin, 50 μg / mL Streptomycin and 0.01 μg/mL NGF-7S.

When the cells had grown for 2 days up to 4 weeks, the experiments were done. Cells were chosen based on size and presence of neurites. Small cells with long processes were used for recording (most likely to be C neurons, with native VR1 receptors).

The cells were recorded with conventional whole cell voltage clamp patch clamp, using the following solutions (calcium ion free):
The extracellular solution comprised (in mM): NaCl 137, KCl 5, $MgCl_2 * H_2O$ 1.2, HEPES 10, Glucose 10, EGTA 5, Sucrose 50, pH to 7.4 with NaOH.
The intracellular solution comprised K-gluconate 140, NaCl 3, $MgCl_2 * H_2O$ 1.2, HEPES 10, EGTA 1, pH to 7.2 with KOH. When the cells were penetrated with suction, a puff of capsaicin (500 nM) was used to determine if the cell expressed VR1 receptor. If not, a new cell was chosen. If yes, then the compounds were added in increasing doses before the capsaicin pulse (500 nM), to determine an IC_{50} value.

List of abbreviations

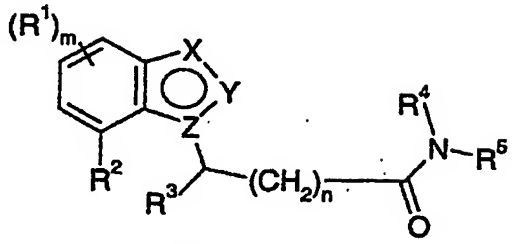
VR1	vanilloid receptor 1
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
GERD	gastro-esophageal reflux disease
DRG	Dorsal Root Ganglion
BSA	Bovine Serum Albumin
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
EGTA	Ethylene glycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid
DMEM	Dulbeccos Modified Eagle's Medium

Results

Typical IC_{50} values as measured in the assays described above are 10 μM or less. In one aspect of the invention the IC_{50} is below 500 nM. In another aspect of the invention the IC_{50} is below 100 nM. In a further aspect of the invention the IC_{50} is below 10 nM.

CLAIMS

1. A compound having the formula I



(I)

wherein:

R^1 is H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 or $CONR^6R^7$;

m is 1, 2, 3 or 4;

R^2 is H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 or $CONR^6R^7$;

X, Y and Z are each independently C, CR^6, N or NR^6;

R^3 is H or C_{0-4}alkyl;

n is 0, 1, 2 or 3;

R^4 is H or C_{0-4}alkyl;

R^5 is H, C_{1-10}alkyl, C_{5-6}aryl, C_{3-7}cycloalkyl, C_{5-6}heteroaryl, whereby any aryl or cycloalkyl may be fused with heteroaryl, C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl;

and R^4 and R^5 may be substituted with one or more A; and

A is H, OH, NO_2, NH_2, CO, O(CO), halo, C_{1-6}alkyl, NR^6R^7, C_{1-6}haloalkyl, C_{1-6}alkylOC_{0-6}alkyl, R^6OC_{1-6}alkyl, R^6CO, CO_2R^6 or $CONR^6R^7$;

R^6 and R^7 are each independently H or C_{1-6}alkyl;

or salts, solvates or solvated salts thereof,

with the proviso the compound is not 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide and 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide.

2. The compound according to claim 1 wherein R^1 is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl;

m is 1 or 2;

R^2 is H, NO_2, NH_2, halo, NR^6R^7, C_{1-6}alkyl or C_{1-6}haloalkyl;
X, Y and Z are each independently C, N or NR^6;
R^3 is H or C_{0-4}alkyl;
n is 0, 1 or 2;
R^4 is H;
R^5 is H, C_{1-10}alkyl, C_{5-6}aryl, whereby any aryl may be fused with heteroaryl;
and R^4 and R^5 may be substituted with one or more A; and
A is H, OH, halo, C_{1-6}alkyl, NR^6R^7, C_{1-6}haloalkyl or C_{1-6}alkylOC_{0-6}alkyl;
R^6 and R^7 are each independently H or C_{1-6}alkyl.

3. The compound according to any one of claims 1 or 2 wherein R^1 is selected from the group consisting of H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}haloalkyl and m is 1 or 2.

4. The compound according to any one of claims 1 to 3 wherein R^2 is H, NO_2, NH_2 or halo.

5. The compound according to any one of claims 1 to 4 wherein X and Z are N and Y is CR^6.

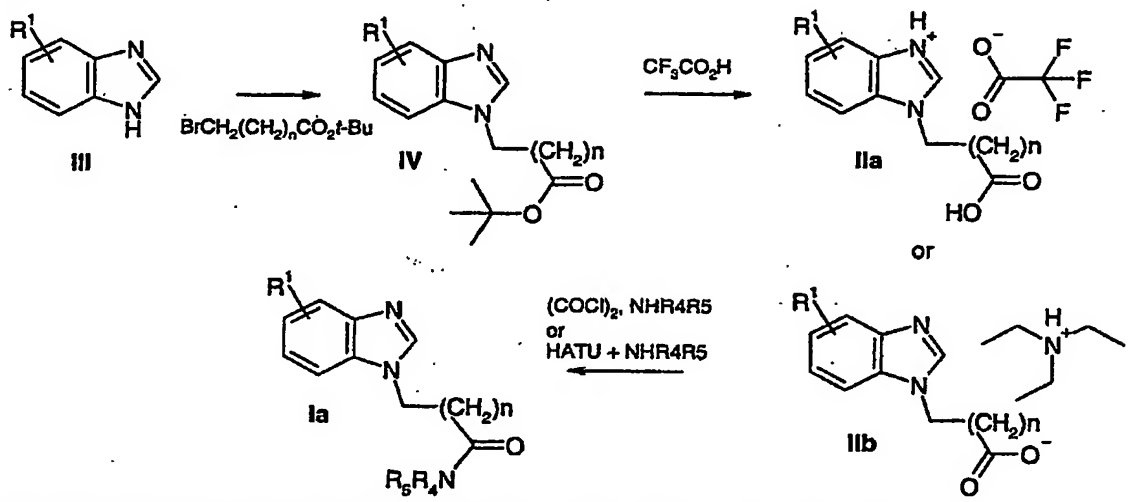
6. The compound according to any one of claims 1 to 5 wherein R^4 is H and R^5 is selected from the group consisting of H, C_{1-10}alkyl and C_{5-6}aryl, whereby any aryl may be fused with heteroaryl.

7. The compounds selected from the group consisting of
2-Benzoimidazol-1-yl-*N*-(3-trifluoromethyl-phenyl)-propionamide,
2-Benzoimidazol-1-yl-*N*-(3-chloro-4-fluoro-phenyl)-acetamide,
2-Benzoimidazol-1-yl-*N*-(3-fluoro-4-methyl-phenyl)-acetamide,
2-Benzoimidazol-1-yl-*N*-(3,4-difluoro-phenyl)-acetamide,
2-(4-Methyl-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,
2-(4,5-Difluoro-benzoimidazol-1-yl)-*N*-(3-trifluoromethyl-phenyl)-acetamide,
2-(6,7-difluoro-benzoimidazol-1-yl)-*N*-(3-trifluoromethyl-phenyl)-acetamide,
2-(4,5- difluoro-benzoimidazol-1-yl)-*N*-(3-trifluoromethyl-phenyl)-acetamide,

2-Benzoimidazol-1-yl-*N*-(3-dimethylamino-phenyl)-acetamide,
2-Benzoimidazol-1-yl-*N*-(4-tert-butyl-phenyl)-acetamide,
2-Benzoimidazol-1-yl-*N*-(3-trifluoromethyl-benzyl)-acetamide,
2-Benzoimidazol-1-yl-*N*-(4-chloro-benzyl)-acetamide,
2-(1*H*-Benzoimidazol-1-yl)-*N*-(3,5-dimethoxyphenyl)acetamide,
3-Benzoimidazol-1-yl-*N*-(4-tert-butyl-phenyl)-propionamide,
4-Benzoimidazol-1-yl-*N*-(4-tert-butyl-phenyl)-butyramide,
2-Benzoimidazol-1-yl-*N*-(2-methyl-benzothiazol-5-yl)-acetamide,
2-Benzoimidazol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide,
2-(4-Amino-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,
2-(6,7-Difluoro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,
2-(5-fluoro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,
2-(6-fluoro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,
2-(1*H*-benzoimidazol-1-yl)-*N*-heptylacetamide,
2-(5-Fluoro-1*H*-indol-3-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide, and
2-(1-Methyl-1*H*-indol-3-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide,
or salts, solvates or solvated salts thereof.

8. A processes for the preparation of the compound according to claim 1, wherein R^1 to R^4, are defined as in claim 1, comprising;

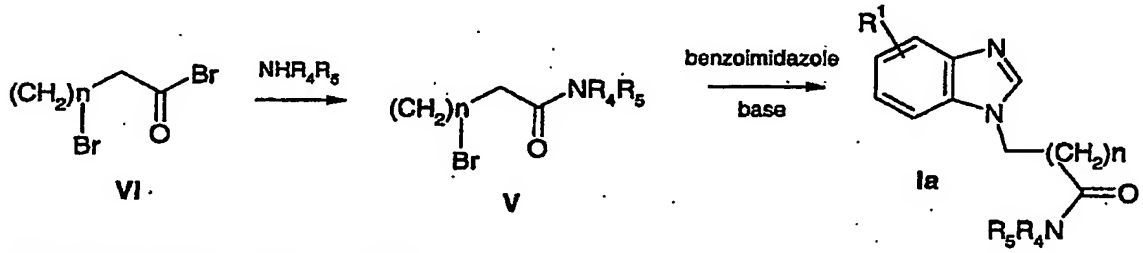
Method A



whereby the target compound of formula Ia is obtained from the acid of formula IIa or its deprotonated form IIb, *via* its conversion into an activated form and futher treatment with an appropriate amine NHR^4R^5,

or,

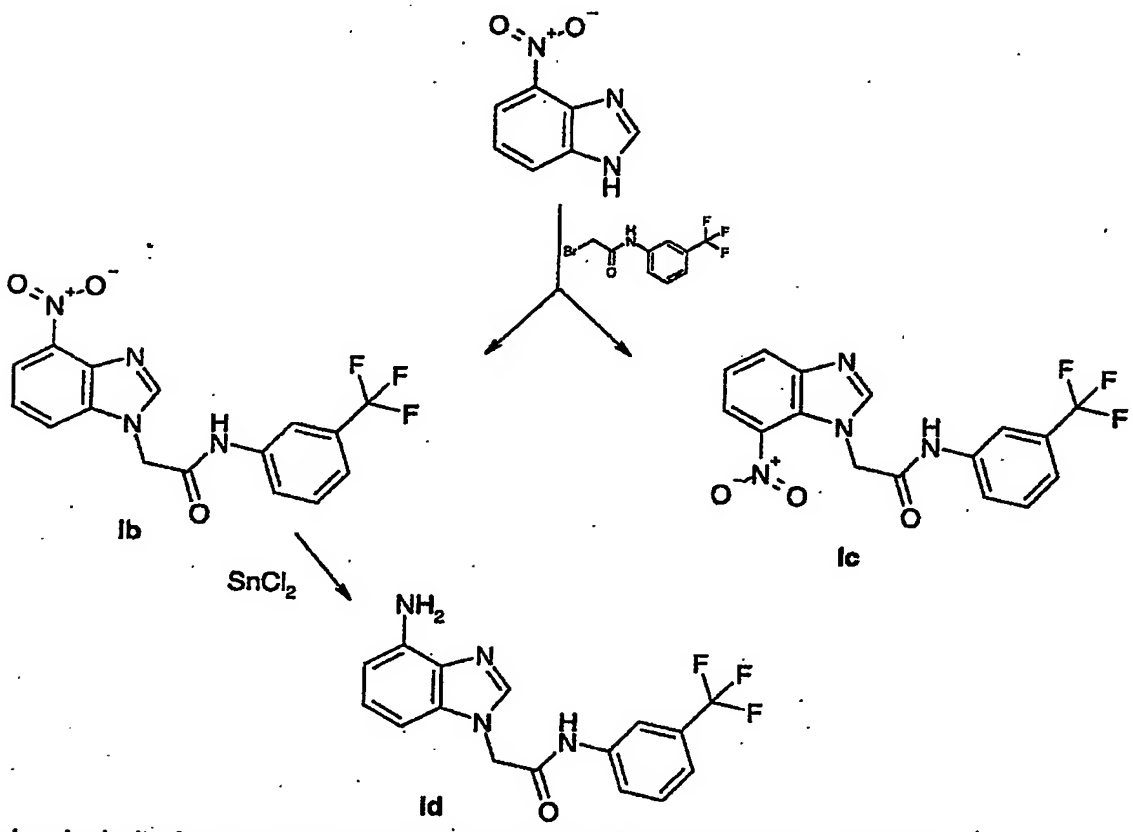
Method B



wherein, the target compound of formula Ia is obtained from an alkylbromide of formula V and an appropriate benzimidazole.

9. A process for purifying mixtures of regioisomers of the compound of formula I, according to claim 1, comprising;

Method C



wherein 4-nitrobenzoimidazole is converted to a mixture of 4-nitro- and 7-nitro-regioisomers of formula Ib and Ic, or the nitro derivative is converted to the corresponding amino derivative of formula Id using an appropriate reducing agent.

10. The compound according to any one of claims 1 to 7, for use in therapy.

11. Use of the compound according to any one of claims 1 to 7, in treatment of VR1 mediated disorders.

12. The use according to claim 11 for treatment of acute and chronic pain disorders.

13. The use according to claim 11 for treatment of acute and chronic inflammatory pain.

14. The use according to claim 11 for treatment of indications selected form the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

15. Use of the compound of formula I according to any one of claims 1 to 7, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

16. A method of treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 7.

17. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 7, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

18. The pharmaceutical formulation according to claim 17, for use in the treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

19. Use of 2-Indol-1-yl-*N*-(3-trifluoromethyl-phenyl)-acetamide and 2-(7-Nitro-1*H*-benzoimidazol-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

20. Use of compounds

2-bromo-*N*-(3-trifluoromethyl-phenyl)-propionamide,

benzoimidazol-1-yl-acetic acid *tert*-butyl ester,

3-carboxymethyl-3*H*-benzoimidazol-1-ium trifluoro-acetate,

2-bromo-*N*-(3-trifluoromethyl-phenyl)-acetamide,

Synthesis of 4-methyl-1*H*-benzoimidazole,

2-Bromo-*N*-(3-dimethylamino-phenyl)-acetamide,

methyl 3-(1*H*-benzoimidazol-1-yl)propanoate ,

3-(1*H*-benzoimidazol-1-yl)propanoic acid,

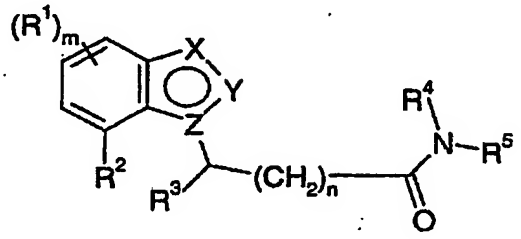
methyl 4-(1*H*-benzoimidazol-1-yl)butanoate, and

4-(1*H*-benzoimidazol-1-yl)butanoic acid,

as intermediates in the preparation of compounds suited for the treatment of VR1 mediated disorders.

ABSTRACT

The present invention relates to new compounds of formula I,



(I)

wherein R^1 to R^5 are as defined as in formula I, or salts, solvates or solvated salts thereof, processes for their preparation and to new intermediates used in the preparation thereof, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy.